REVELATION® Tx Microcatheter Ablation System (P020039)
Cardima, Inc.

EXPERT CONSULTANT MEMORANDUM

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As clinicians specializing in the field of electrophysiology, we are writing this document in order to offer our perspective on the clinical utility of the REVELATION® Tx Microcatheter Ablation System for right atrial (RA) ablation in the management of symptomatic atrial fibrillation (AF). The results of the multi-center study have been peer-reviewed and published,[1] and approval awaits the result of the upcoming Medical Device Dispute Resolution Panel. We are supportive of this product, and believe it has a role in clinical practice.

As you are aware, in 2006 the three major cardiology societies in the US and Europe issued a joint position paper elevating ablation to second line status for AF treatment, after only one drug failure. This was controversial then, and remains controversial now, in part because there is no consensus regarding lesion set, and no approved catheter system for AF. More specifically, current efforts aimed at creating linear lesions in the left atrium have been handicapped by significant complication rates, the need for repeat procedures, disappointing long-term results and "drag and burn" hot tip technology not ideally suited for making linear lesions. Nevertheless, most thought leaders in electrophysiology (EP) believe ablation offers a significant benefit to the many patients who develop side effects or do not benefit from currently available anti-arrhythmic medications.

The concept of creating uninterrupted, transmural linear lesions in the RA addresses the state of multiple wavelets of reentry defining AF, by modifying the atrial substrate. It evolved from the work of Alessie and colleagues in the Netherlands, and was shown to work in versions of the surgical maze procedure pioneered by Cox. Cardima developed a linear ablation catheter (REVELATION® Tx) to replicate this success with a catheter-based radiofrequency approach. Although other companies initially invested in this sort of trial, to the best of our knowledge, Cardima is the only company that saw its study through to completion.

The finding of AF "triggers" by Haissaguerre and co-workers[2] led to a significant shift in much of the research in curative ablation of AF, focusing on the pulmonary veins and left atrium. However, this does not negate the contribution of reentry in maintaining AF. The surgical literature, clinical research (in particular by Dr. Abe Kocheril), and the Cardima multi-center experience show that much symptomatic benefit can be achieved by RA linear ablation as part of the treatment paradigm.

Several of us have served as study investigators and are familiar with the various challenges associated with this type of trial. However, it is our opinion that some of

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[1] Kocheril AG, Calkins H, Sharma AD, Cher D, Stubbs HA, Block JE. 2005. Hybrid therapy with right atrial catheter ablation and previously ineffective antiarrhythmic drugs for the management of atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology* 12:189–197.

[2] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. 1998. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *New England Journal of Medicine* 339:659–666.

the issues raised by FDA regarding this trial may be out of proportion with the potential value of this device to patients who suffer AF. Specifically, one major concern raised by FDA relates to the use of off label catheters for ablation of the tricuspid isthmus (the "flutter line"). The REVELATION® Tx Microcatheter was not intended to be used in thick, trabeculated cardiac tissue and was therefore never intended for use in ablating the isthmus. Typically, flutter ablation is performed with single tip or "hot tip" catheters and is considered a standard EP procedure. At the time of the REVELATION® Tx Microcatheter Ablation System trial, investigators felt that prevention of flutter might be necessary and that isthmus ablation should be performed at the same time that the REVELATION® Tx Microcatheter was used for RA ablation. Since there were no FDA approved catheters indicated for treating the flutter line, Cardima developed the NAVABLATOR® to fill this void during the study, although the protocol allowed for the use of an "operator choice" device for this line only. We no longer perform flutter lines in AF ablation, and we are convinced that the manner in which the flutter line was treated has no bearing upon the clinical results generated by the REVELATION® Tx Microcatheter Ablation System in treating AF. We strongly believe this is a non-issue.

An additional FDA concern has been the lack of a clearly defined procedural end-point, making it difficult to evaluate early success or failure, and making it difficult to teach the technique to other EPs. In our minds this also is a non-issue. Both Drs. Kocheril and Calkins have indicated that electrograms are easy to see and read, and that the procedure is both easy and fast to perform.[3] This procedure would seem to be much simpler and safer, with a shorter learning curve, than what is currently being promoted in the left atrium.

During the study, EPs in general and study investigators specifically did not recognize or appreciate the fact that early post-ablation AF recurrences are not reliable predictors of later AF. Many of the medication changes and repeat procedures in the study could be avoided today because we now know that it is important to wait 3 months before evaluating treatment success. In current trials of AF ablation, early recurrences typically are not considered treatment failures, and a 3-month blanking period has become standard. Additionally, as per protocol, some medication changes were made due to drug intolerances or interactions, such as switching from a beta-blocker (Sotalol) to another medication in order to avoid sinus bradycardia, which is often associated with AF and the tachy/brady syndrome. Most importantly, there is absolutely no evidence to suggest that patients like those enrolled in the trial (AF for average 5 years, failed 2.9 AADs, average 9 episodes of PAF the month leading into the ablation) would suddenly become "drug successes."

We concur with the suggestion made by FDA in the guidance document on clinical study designs for percutaneous catheter ablation for treatment of atrial fibrillation

[3] Circulatory System Devices Panel meeting transcript. May 29, 2003:170(2), 232(4).

(January 2004)[4] about the value of single-arm trials, especially with device therapies, and allowing for reasonable input of non-randomized control data (such as historical data or patients as their own control) when it comes to AF. "Atrial fibrillation begets atrial fibrillation." This is one of the most difficult and pressing issues in cardiology today. We feel that using sham interventional procedures as controls in this patient population would be suboptimal and fraught with great challenges, and that a second large and prolonged clinical trial evaluating the REVELATION® Tx Microcatheter Ablation System against "failed" drug therapy seems inappropriately burdensome.

As noted above, currently all catheter ablation for AF is off label using catheter products not designed or clinically tested for use in AF. The Cardima catheter provides the first opportunity for an approved catheter for the treatment of AF. The public health need for safe and effective treatments for AF is large. Left atrial catheter ablation is currently not standardized and is not regulated by FDA. Moreover, left atrial catheter ablation has known severe complications. FDA's approval of the REVELATION® Tx Microcatheter Ablation System would allow more oversight and regulation of catheter ablation and for the procedure to be performed safely "on label." The risks of pulmonary vein stenosis, strokes, esophageal fistulae and the difficulties, in general, of transseptal left atrial ablation have kept many electrophysiologists from offering ablation to their patients. We as a field have underestimated the clinical effects of substrate modification by RA linear ablation, in our rush to ablate the pulmonary veins and left atrium. The Cardima trial has shown this catheter to be safe and effective. Moreover, the catheter has been easy to use, despite the differences from conventional designs. The FDA has audited the Cardima study at the Carle Heart Center and at Johns Hopkins Hospital. Dr. Kocheril was told that his data were of good quality at the exit interview. We trust that the integrity of the data will help in the process of evaluating the catheter for approval.

In our view, safety issues are paramount. Beyond that, no one trial will ever be enough in itself to demonstrate a curative lesions-set. This linear system should be approved so that multiple centers can ablate in the RA without fear of leaving incomplete lines, adding this procedure to what they already are doing on the left if so desired, to hopefully provide patients with a more effective procedure sooner rather than later. We are satisfied that safety is not a major concern with this system, and we are under the impression that the FDA agrees.

The medical literature on AF continues to evolve. It is becoming clear that the pathophysiology of AF is complex, involving multisite triggers, complex re-entrant circuits, highly variable anatomy and even a role for autonomic tone. Because the pathophysiology of AF is complex, it is highly likely that ablation treatment approaches will be complex as well. It seems shortsighted to us that FDA appears to

[4] Guidance for Industry and FDA Staff: Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation. US Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, January 9, 2004.

require a single catheter to produce high effectiveness rates, i.e., a “one size must fit all” approach. As AF ablation techniques continue to evolve, it is likely that multiple tools will eventually be used in treating AF. In our opinion, the Cardima system appears to have met the criteria for safety and effectiveness and may end up being just one of the tools used in the “final” procedure.

Cardima has played an integral role in the advance of electrophysiology in treating AF through the REVELATION® Tx Microcatheter Ablation System study, multiple educational programs to exchange ideas on curative ablation approaches, and in developing other products to assist investigative centers to overcome hurdles in this important area. Approval of this PMA will allow Cardima to exist as a company and continue to help the field. Every expert on AF ablation, worldwide, has had interactions with Cardima. A version of the system has been approved in Europe for left atrial ablation, and currently trials in England and Italy are ongoing and have demonstrated safety and efficacy along with ease of use and shorter procedure times than competing hot tip systems. A surgical version has been approved in the US and used open heart in over 45 patients at Lenox Hill, and is currently being studied by Dr. Adam Saltman at Maimonides Medical Center for surgical ablation using standard laparoscopic/thoracoscopic techniques (system approved).

As clinicians, we need tools with which to help our patients with AF. We are surprised that it is taking so long for the REVELATION® Tx Microcatheter Ablation System to gain FDA approval for clinical use. It is a unique technology that is at risk of lapsing into oblivion, and yet there are more data available on it than the catheters that clinicians use currently for treating AF.